LISTING OF CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in this application.

1. (currently amended) A method ~~for~~ of using parallel computational means to determine~~ing~~ the three-dimensional structure of a molecule of interest from experimental X-ray diffraction data for a crystal of said molecule of interest, which comprises

~~(a) obtaining x-ray diffraction data for crystals of said molecule of interest;~~

~~(b)~~ (a) selecting as a basis set an orthogonal set of at least one spherical harmonic spherical Bessel basis function[[s]] to represent the three dimensional electron density in said crystal, thereby generating a spherical harmonic spherical Bessel model, such that the number of degrees of freedom in the ~~modeled~~ electron density of the model is reduced relative to the number of ~~measured~~ experimental data;

~~(c)~~ (b) determining the maximum minimal resolution of said spherical harmonic spherical Bessel model to be used to determine the three-dimensional structure of said molecule of interest;

(d) (c) determining a radius and position for a spherical asymmetric unit in a model crystal lattice as derived from said experimental X-ray diffraction data for said crystal[[s]];

(e) (d) determining a computationally efficient grouping of x-ray diffraction intensities for the positioning of at least one spherical harmonic spherical Bessel basis function;

(f) (e) modifying[[,]] each said at least one spherical harmonic spherical Bessel basis function within the selected basis set selected in (a) such that it represents an individual basis function centered at a specific position and becomes a Fourier representation of a positionally translated basis function;

(g) (f) calculating said at least one Fourier representation of the a full-unit cell, symmetry-expanded spherical harmonic spherical Bessel basis function for each basis function in the basis set chosen selected in (a) (b);

(h) (g) determining at least one complex-valued coefficient of said spherical harmonic spherical Bessel series basis function by comparing said full-unit cell, symmetry-expanded spherical harmonic spherical Bessel basis function determined calculated in (g) (f) with said experimental x-ray diffraction data, wherein scale factors and correlation coefficients of the phase angle of said complex-valued

coefficient are calculated at any one of the set of presumed values 0° and 90°;

~~(i)~~ (h) using said at least one complex-valued coefficient of each spherical harmonic spherical Bessel basis function in the basis set selected in (a) for said spherical harmonic spherical Bessel ~~series~~ basis function to iteratively update a phased Fourier representation of the three[[3]]-dimensional electron density of ~~the~~ said crystal; ~~and~~

~~(j)~~ (i) calculating Fourier summations based on a combination of said phased Fourier representation and the ~~experimental~~ x-ray diffraction intensities to obtain an interpretable [[3]]three-dimensional representation of the contents of the full-unit cell; and

(j) outputting said three-dimensional representation to a suitable output hardware.

2. (currently amended) The method of claim 1, further comprising, subsequent to step (i), the additional steps of:

~~(k)~~ (j) determining a three-dimensional model~~ed~~ structure of [[a]] said ~~diffracting~~ molecule of interest ~~wherein a three-dimensional model structure of said molecule of interest~~ by ~~using~~ computational graphical model fitting; and

~~(l)~~ (k) subjecting said three-dimensional model structure to improvements by simulated annealing, least

squares, maximum entropy, and/or Bayesian data analysis and/or molecular mechanics energy minimizations.

3. (currently amended) The method of claim 1, wherein said radius and position for [[a]]said spherical asymmetric unit is known.

4. (currently amended) The method of claim 1, wherein said radius and position for [[a]]said spherical asymmetric unit is not known.

5. (currently amended) The method of claim 4, further comprising, prior to step (j), the step of determining calculation of said radius and position of said the largest spherical asymmetric unit that can fit into a predetermined crystal lattice without overlap.

6. (currently amended) The method of claim 5, further comprising, prior to step (j), the step of determining the numerical value of the angular increment between each trial value estimated for the phase angle of coefficient of a spherical harmonic spherical Bessel component basis function of a model generated from said largest spherical asymmetric unit said model of said largest spherical asymmetric unit.

7. (currently amended) The method of claim 5, further comprising, prior to step (j), the step of determining the value of the complex-valued coefficient of said spherical harmonic spherical Bessel basis function coefficient.

8. (currently amended) The method of claim 1, further comprising, prior to step (j), the step of determining the total number of m-indices to be provided ~~in~~ to a recursive calculation.

9. (currently amended) The method of claim 1, further comprising, prior to step (j), the step of determining a starting and a final value of an arbitrary exponent by which power to raise the values of said calculated correlation coefficients to allow iterative improvement of the ~~modeled~~ electron density of the model.

10. (currently amended) The method of claim 1, further comprising, prior to step (j), the step of determining said at least one spherical Bessel function ~~of~~ together with ordinate values of a Bessel function argument such that the zeroes of these Bessel functions are calculated.

11. (currently amended) The method of claim 8, further comprising, prior to step (j), the step of converting said ~~diffraction~~ m-indices to spherical coordinates and ~~initialing~~ initializing said numerical values associated with said ~~diffraction index~~ m-indices to allow later recursive calculation of a value of each spherical harmonic spherical Bessel basis function at said ~~diffraction~~ m-indices.

12. (currently amended) The method of claim 11, further comprising, prior to step (j), the step of executing a recursive program cycle wherein unphased diffraction amplitudes

are converted to a Fourier transform of a calculated model of a portion of [[a]] said ~~crystal~~ full-unit cell.

13. (withdrawn) The method of claim 1, wherein the results of said method can be further used to accurately predict the identity of ligands or to assess the relative binding affinity of said ligands to said molecule of interest.

14. (currently amended) The method of claim 1, wherein ~~the process for carrying out the elements of~~ said method for determining the three-dimensional structure of [[a]] said molecule of interest[[,]] is ~~contained in~~ carried out by a computer, said computer being capable of receiving data and performing said method.

15. (currently amended) The method of claim ~~15~~ 14, wherein said computer is coupled to a display device and there exists a means for presenting the chemical or molecular structural characteristics of said at least one molecule of interest on said display device.

16. (original) The method of claim 1, wherein said at least one molecule of interest is selected from the group consisting of:

a)   a pharmaceutical;

b)   an enzyme;

c)   a catalyst;

d)   a polypeptide;

e)   an oligopeptide;

f)   a carbohydrate;

g)   a nucleotide;

h)   a macromolecular compound;

i)   an organic moiety of an alkyl, cycloalkyl, aryl, aralkyl or alkaryl group or a substituted or heterocyclic derivative thereof;

j)   an industrial compound;

k)   a polymer;

l)   a monomer;

m)   an oligomer;

n)   a polynucleotide;

o)   a multimolecular aggregate; and

p)   an oligopeptide.

17. (currently amended) The method of claim 1, wherein the chemical characteristics of said molecule of interest are in the form of a three dimensional representation, said three dimensional representation allowing the identification of the ~~molecular~~ features of said ~~molecular~~

~~object~~ molecule of interest such that said representation could be used to determine desirable chemical characteristics of said ~~at least one~~ molecule of interest.

18. (currently amended) The method of claim 1, wherein the structural characteristics of said molecule of interest are in the form of a three dimensional representation, said three dimensional representation allowing the identification of the ~~molecular~~ features of said ~~molecular object~~ molecule of interest such that said representation could be used to determine structural characteristics of said ~~at least one~~ molecule of interest that could be modified.

19. (original) The method of claim 1, wherein said method is further utilized to predict the chemical activity of at least one molecule of interest.

20. (original) The method of claim 1, wherein said method is further utilized to predict the biochemical activity of at least one molecule of interest.

21. (original) The method of claim 1, wherein said method is further utilized to predict the physiological activity of at least one molecule of interest.

22. (currently amended) The method of claim 1, further comprising depicting a three-dimensional structure of said molecule of interest from the summation of said at least one Fourier representation.

23. (currently amended) The method of claim 22, further comprising generating a three-dimensional model structure of said molecule of interest from said three-dimensional structure of said molecule of interest from the summation of said at least one Fourier representation.

Claim 24 (previously canceled).

Claim 25 (previously canceled).

Claim 26 (previously canceled).

Claim 27 (previously canceled).

Claim 28 (previously canceled).

Claim 29 (previously canceled).

Claim 30 (previously canceled).

Claim 31 (previously canceled).

Claim 32 (previously canceled).

Claim 33 (previously canceled).

Claim 34 (previously canceled).

Claim 35 (previously canceled).

Claim 36 (previously canceled).

37. (currently amended) The method of claim 1, wherein said x-ray diffraction data for said crystal[[s]]

further comprises data representing the crystal space group,
the crystal symmetry operators, the crystal lattice dimensions
and angles, the maximum resolution of the experimental
diffraction data, the experimentally measured values of the x-
ray diffraction intensities, the derived values of the x-ray
structure factor amplitudes, and an input value chosen from the
maximum minimal resolution of the spherical harmonic[[,]]
spherical Bessel (SHSB) model of said molecule of interest.

Claim 38 (previously canceled).

39. (currently amended) The method of claim 1,
further comprising, prior to step (j), the step of inputting a
numerical value for the angular increment between each trial
value presumed for the phase angle of coefficient of the
complex-valued coefficient of said individual origin-centered
spherical harmonic spherical Bessel basis function (SHSB)
coefficient .

40. (currently amended) The method of claim
[[1]] 39, further comprising, prior to step (j), the step of
determining an appropriate value of said angular increment
automatically for each phase angle of coefficient of the
complex-valued coefficient of said individual origin-centered
spherical harmonic spherical Bessel basis function (SHSB)
coefficient .

41. (currently amended) The method of claim 1, further comprising:—, subsequent to step (i), the additional steps of:

~~(k)~~ (j) determining, from the input limiting resolution for the ~~origin-centered~~ spherical harmonic spherical Bessel model, the extent of the indices *lmn* of the ~~component SHSB~~ spherical harmonic spherical Bessel basis function[[s]] that are required for said molecule of interest[[,]];

~~(l)~~ (k) converting diffraction indices (hkl) to spherical coordinates[[,]];

~~(m)~~ (l) initializing some numerical values associated with each diffraction index to allow later recursive calculation of the value of each spherical harmonic spherical Bessel basis function at each hkl index;—and

~~(n)~~ (m) executing a recursive program cycle.

42. (currently amended) The method of claim 41, further comprising:—, subsequent to step (m), the additional steps of:

~~(o)~~ (n) inputting the observed experimental diffraction amplitudes for each hkl index in the Fourier representation;

~~(p)~~ (o) converting a set of ~~SHSB~~ spherical harmonic spherical Bessel coefficients to at least one Fourier representation; and

~~(q)~~ (p) combining the contributions from the l, m, and n components of said at least one Fourier representation of the ~~origin-centered, individual~~ ~~SHSB~~ spherical harmonic spherical Bessel basis function to provide a full [[3]]three-dimensional Fourier representation of the ~~origin-centered individual SHSB~~ spherical harmonic spherical Bessel basis function of said molecule of interest.

43. (original) The method of claim 1, further comprising, prior to step (j), the step of writing information concerning the three dimensional Fourier representation of the model of said crystal of said molecule of interest to an electronic record keeper, thereby storing the spherical harmonic spherical Bessel model, including the Fourier representation of each stored ~~SHSB~~ spherical harmonic spherical Bessel model such that it may be read at the beginning of the calculation for the next packet of m-values for the ~~SHSB~~ m-indices.

44. (currently amended) The method of claim 1, wherein the steps and calculations necessary for ~~the~~ ~~determination of the depiction~~ rendering the three-dimensional representation of said molecule of interest[[s]] ~~is~~ are capable of being recorded in an electronic medium.

45. (currently amended) The method of claim 1, wherein the steps and calculations necessary for the ~~determination of the depiction~~ rendering the three-dimensional representation of said molecule of interest[[s]] ~~is~~ are recorded in an electronic medium ~~are~~ and stored in a secondary storage device.

46. (currently amended) The method of claim 1, wherein said ~~method includes a display device such as~~ suitable output hardware is a monitor.

47. (currently amended) The method of claim 43, wherein said method further provides a ~~backup memory~~ computational means to record the steps of the method, ~~and calculations~~ wherein said means is selected from the group consisting of:

    a)   a floppy disk;

    b)   a second hard disk drive;

    c)   a read/write compact disc;

    d)   magnetic tape;

    e)   a Bernoulli Box;

    f)   a Zip disk; and

    g)   other means for storing electronic data.

48. (currently amended) A method ~~for~~ of using parallel computational means to determin~~e~~ing the three-dimensional structure of a molecule of interest from experimental X-ray diffraction data for a crystal of said molecule of interest, ~~which comprises~~ comprising the steps of:

~~(a) obtaining x-ray diffraction data for crystals of said molecule of interest;~~

~~(b)~~ (a) choosing, as the basis set, an orthogonal set of at least ~~one, but more often several~~ one spherical harmonic spherical Bessel basis function[[s]] to represent the three[[3]]-dimensional electron density in the crystal, thereby generating a spherical harmonic spherical Bessel model, such that the number of degrees of freedom in the ~~modeled~~ electron density of the model is reduced relative to the number of ~~measured~~ experimental data;

~~(c)~~ (b) determining the maximum minimal resolution of said spherical harmonic spherical Bessel model to be used to determine the three-dimensional structure of said molecule of interest;

~~(d)~~ (c) determining a radius and position for a spherical asymmetric unit in a model crystal lattice as derived from said diffraction data for said crystal[[s]];

~~(e)~~ (d) determining a computationally efficient grouping of x-ray diffraction intensities for the positioning

of at least one spherical harmonic spherical Bessel basis
function;

(f) (e) modifying, in turn, each said at least one
spherical harmonic spherical Bessel basis function within the
selected basis set such that it represents an individual basis
function centered at a specific position and becomes a Fourier
representation of a positionally translated basis function;

(g) (f) calculating said at least one Fourier
representation of the a full-unit cell, symmetry-expanded
spherical harmonic spherical Bessel basis function for each
basis function in the basis set chosen in (a) (b);

(h) (g) determining the at least one complex-valued
coefficient[[s]] of said spherical harmonic spherical Bessel
basis function series by comparing said full-unit cell,
symmetry-expanded spherical harmonic spherical Bessel basis
function determined in (f) (g) with said experimental x-ray
diffraction data, wherein scale factors and correlation
coefficients of the phase angle of said complex-valued
coefficient are calculated at any one of the set of presumed
values 0° and 90°;

(i) (h) using said determined coefficients of each
spherical harmonic spherical Bessel function in the basis set
for said spherical harmonic spherical Bessel series function to
update iteratively a phased Fourier representation of the
[[3]]three-dimensional electron density of the crystal; and

~~(j)~~ (i) calculating Fourier summations based on a combination of said phased Fourier representation and the ~~experimental~~ x-ray diffraction intensities to obtain an interpretable [[3]]three-dimensional representation of the contents of ~~the~~ said full-unit cell; and

(j) outputting said three-dimensional representation to a suitable output hardware;

wherein the chemical characteristics of said molecule of interest are in the form of a three dimensional representation, said three dimensional representation allowing the identification of the molecular features of said ~~quantum object~~ molecule of interest such that said representation could be used to alter ~~to~~ the chemical characteristics of said ~~at least one~~ molecule of interest.

49. (canceled) The method of claim 48 wherein said spherical harmonic model to be used is the spherical Bessel mode.

50. (currently amended) The method of claim 48, wherein said radius and position for [[a]] said spherical asymmetric unit is known.

51. (currently amended) The method of claim 48, wherein said radius and position for [[a]] said spherical asymmetric unit is not known.

52. (original) The method of claim 48, further comprising the step of writing information concerning the three dimensional structure of said molecule of interest to an electronic record keeper, the Fourier representation of each stored ~~SHSB~~ spherical harmonic spherical Bessel model such that it may be read at the beginning of the calculation for the next packet of m-values for the ~~SHSB~~ m-indices.

53. (currently amended) The method of claim 48, wherein the steps and calculations necessary for ~~the~~ determination of the ~~depiction~~ representation of said molecule of interest[[s]] is capable of being recorded in an electronic medium.

Claim 54 (previously canceled).

Claim 55 (previously canceled).

Claim 56 (previously canceled).

Claim 57 (previously canceled).

Claim 58 (previously canceled).

Claim 59 (previously canceled).

Claim 60 (previously canceled).

61. (currently amended) The method of claim 48, wherein the chemical characteristics of said molecule of interest are in the form of a three dimensional representation,

said three dimensional representation allowing the identification of the molecular features of said <u>molecule of interest</u> ~~quantum object~~ such that said representation could be used to alter to the chemical characteristics of said ~~at least one~~ molecule of interest.

62. (original) The method of claim 48, wherein said method is further utilized to predict the chemical activity of at least one molecule of interest.

63. (withdrawn) A method of drug design comprising the step of using the three-dimensional structure of a molecule of interest as determined by the method of claim 1, to computationally evaluate a chemical entity for associating with the active site of a molecule of interest.

64. (withdrawn) The method according to claim 63, wherein said chemical entity is a competitive or non-competitive inhibitor of said molecule of interest.

65. (withdrawn) The method of drug design according to claim 63 comprising the step of using the structure coordinates of said molecule of interest to identify an intermediate in a chemical reaction between said molecule of interest and a compound which is a substrate or inhibitor of said molecule of interest.

66. (withdrawn) The method of drug design according to claim 63, wherein said chemical entity is an

inhibitor of said molecule of interest and is selected from a database.

67. (withdrawn) The method according to claim 63, wherein said chemical entity is designed de novo.

68. (withdrawn) The method according to claim 63, wherein said chemical entity is designed from a known inhibitor of said molecule of interest.

69. (withdrawn) The method according to claim 63, wherein said step of employing said three-dimensional structure to design or select said chemical entity comprises the steps of:

(a) identifying molecules or molecular fragments capable of associating with molecule of interest as determined by the method of claim 1; and

(b) assembling the identified molecules or molecular fragments into a single modified molecule to provide the structure of said chemical entity.